Remarks

Reconsideration and withdrawal of the objections to the specification and the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 17-18 and 21 are amended, claims 6-7 are canceled, and claims 32-35 are added; as a result, claims 1-5 and 8-35 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application.

Amended claims 1, 17-18 and 21 are supported by originally-filed claims 1, 17-18 and 21, respectively, and originally-filed claim 7.

New claims 32-35 are supported by originally filed claims 1, 9-10, 17-18, and 21 and Figure 10.

The specification is amended at pages 1 and 10 to address the objections at page 2 of the Office Action and correct typographical errors.

The Examiner provisionally rejected claims 1-8, 11-16, 18-28, and 31 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-26 of copending application Serial No. 09/825,129. A Request to Expressly Abandon Serial No. 09/825,129 is filed on even date herewith, thereby addressing the § 101 rejection.

The Examiner rejected claims 1, 5-8, 11-13, 15, 17-19, 21-22, 25, and 27-28 under 35 U.S.C. § 103(a) as being unpatentable over U.S. patent publication No. 2002/0193326 (Sukhatme). The Examiner also rejected claims 1, 5-8, 11-13, 15-19, 21-22, and 25-28 under 35 U.S.C. § 103(a) as being unpatentable over U.S. patent publication No. 2002/0193326 in view of Applicant's alleged admission on pages 2 and 26 of the specification. The Examiner further rejected claims 1-8, 11-16, 18-22, 25-28, and 31 under 35 U.S.C. § 103(a) as being unpatentable over U.S. patent publication No. 2002/0193326 in view of Arap et al. (Science, 279:377 (1996)) and Applicant's alleged admission on pages 2 and 26 of the specification. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

Sukhatme is generally directed to methods of inhibiting proliferative diseases characterized by increased production of TGF-β and angiogenic activity (paragraph 0006, lines 1-5), i.e., TGF-β mediated angiogenic activity (paragraph 0006, lines 12-15). It is disclosed that TGF-β mediated angiogenesis can be inhibited with a molecule such as an anti-TGF-β antibody, a TGF-β antagonist, a soluble form of the TGF-β receptor, an antisense TGF-β oligonucleotide, or a molecule that blocks the interaction of TGF-β with receptors (paragraph 0008), as TGF-β1 directly inhibits the resolution phase of endothelial cell growth and migration (paragraph 0028, lines 5-9). It is also disclosed that such molecules can be used in combination with one or more additional antiangiogenic molecules, e.g., angiostatin, endostatin or restin, or fragments thereof (paragraphs 0009 and 0123). Endostatin is disclosed as an inhibitor of the initiation phase of angiogenesis which may be additive or synergistic with agents which inhibit TGF-β-mediated angiogenesis (paragraph 0123).

It is further disclosed that the invention includes fusion and chimeric proteins comprising an antiangiogenic protein, which may be prepared by recombinant means, that can be made up of a combination of two or more antiangiogenic proteins (e.g., angiostatin and endostatin) or an antiangiogenic protein in combination with a targeting agent (e.g., endostatin with epidermal growth factor or RGD peptides) (paragraph 0046, lines 11-21). Sustained release delivery systems are also disclosed (paragraph 0082).

Example 5 in Sukhatme shows that the administration anti-TGF-β antibodies to athymic mice implanted with RCC tumor cells resulted in a decrease in tumor size, possibly due to a decrease in the number of microvessels in the treated group.

Sukhatme does not disclose or suggest a chimeric polypeptide having of an antiangiogenic polypeptide with a targeting moiety at the C-terminus, or that such a chimeric polypeptide would be more potent than a corresponding unmodified antiangiogenic polypeptide, e.g., when present in a sustained release dosage form comprising alginate (see Figures 6 and 9 in Applicant's specification).

Applicant's admissions at pages 2 and 26 of the specification are that kringle 5 of plasminogen, angiostatin (kringle 1-4 of plasminogen), tumstatin, canstatin, anti-thrombin fragment and retinal pigment derived factor, and alginate polymers, are known.

Arap et al. disclose that three peptides motifs, RGD, NGR and GSL, were identified by *in vivo* selection of phage peptide libraries for peptides that home to the vasculature (pages 377-8). RGD-4 (CDCRGDCFC) and CNGRC (a NGR peptide) were cyclized and then conjugated to doxorubicin, a drug with anti-angiogenic activity (page 378 and footnote 18). The conjugates or doxorubicin alone were administered to mice bearing tumors from MDA-MB-435 human breast carcinoma cells (page 374). The doxorubicin-RGD-4C conjugate treated mice outlived the doxorubicin treated mice, had smaller tumors, less spreading to regionally lymph nodes, and fewer pulmonary metastasis (pages 378-9). It is disclosed that similar efficacy was observed with the CNGRC-doxorubicin conjugate (page 379). The authors note that the efficacy of the CNGRC conjugate may be derived entirely from vascular targeting because NGR peptides do not bind to MDA-MD-435 cells (page 380).

Arap et al. do not disclose or suggest a composition in which a targeting moiety is linked to the C-terminus of an antiangiogenic peptide, a host cell transformed with recombinant DNA encoding a chimeric polypeptide having a peptide or polypeptide targeting moiety specific for endothelial cells linked to the C-terminus of an antiangiogenic polypeptide, or methods of using such a chimeric polypeptide.

The Examiner asserts the only difference between Sukhatme and the claimed invention is that the reference does not specifically make the chimeric protein using recombinant techniques, and in view of the explicit suggestion in the Sukhatme to make such proteins using recombinant techniques, it would have been obvious to one of ordinary skill in the art at the time of Applicant's invention to make the claimed fusion proteins. The Examiner also asserts that in view of Sukhatme and Applicant's admission, it would have been obvious to use alginate beads in a sustained release composition, with any known antiangiogenic protein instead of endostatin or angiostatin in the fusion protein. The Examiner further asserts that, in view of Sukhatme, Applicant's admission, and Arap et al., it would have been obvious to one of ordinary skill in the art at the time of Applicant's invention to use either NGR-containing peptides or RGD-containing peptides to deliver endostatin or angiostatin to the tumor.

The art worker in possession of the cited art would be apprised that antiangiogenic agents can inhibit one of two phases in angiogenesis, initiation and resolution

However, none of the cited references or Applicant's admissions alone, or in combination, teach or suggest a chimeric polypeptide having an antiangiogenic polypeptide with a targeting moiety at the C-terminus. Nor do the cited references provide a reasonable expectation that a C-terminally modified endostatin is necessarily more potent than wild-type endostatin.

Accordingly, withdrawal of the § 103(a) rejections is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney ((612) 373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743

Respectfully submitted,

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Date October 29, 2003

By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of October, 2003.

Dawn M. Poole
Name

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Signature